Primary results from OUTREACH: a phase 2 study of lisocabtagene maraleucel administered in the community setting as outpatient or inpatient treatment in patients with relapsed or refractory large B-cell lymphoma

CT-045

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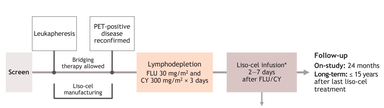
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Introduction

- In the United States (US), ~70% of patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) receive treatment at community/nonuniversity medical centers where outpatient cancer therapy is common[1]
- Chimeric antigen receptor (CAR) T cell therapies are generally administered as inpatient treatment at university medical centers owing to concerns of adverse event (AE) management, including cytokine release syndrome (CRS) and neurological events (NE)[2,3]
- Prospective safety/efficacy data for CAR T cell therapy infusion and monitoring at community sites and in the outpatient setting are of interest
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR$^+$ T cells[4]
- Liso-cel has demonstrated meaningful efficacy (objective response rate [ORR], 73%; complete response [CR] rate, 53%) and low incidences of severe CRS (2%) and NEs (10%) as third-line or later (3L+) treatment for patients with R/R LBCL in the TRANSCEND NHL 001 study (TRANSCEND; NCT02631044)[4]
- Here, we present primary analysis results from the OUTREACH study (NCT03744676), which evaluated liso-cel as 3L+ treatment in patients with R/R LBCL across outpatient and inpatient settings at community medical centers in the US (**Figure 1**)[5]

Methods

Figure 1. OUTREACH study design and key endpoints[6]



KEY PATIENT ELIGIBILITY CRITERIA
- LBCL after ≥ 2 lines of prior therapy
- Prior autologous HSCT allowed
- ECOG PS of 0–1
- Secondary CNS lymphoma allowed
- CrCl > 30 mL/min/1.73 m²
- LVEF ≥ 40%
- No minimum ALC, ANC, platelets, or hemoglobin

Infusion and monitoring setting at investigator's discretion (N = 82)
- Outpatient setting (n = 57)
- Inpatient setting (n = 25)

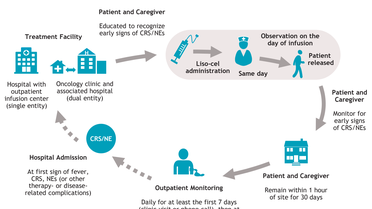
PRIMARY ENDPOINT
- Incidence of grade ≥ 3 CRS, NEs, prolonged cytopenias at Day 29, and infections

SECONDARY ENDPOINTS
- AEs, ORR, CR rate, DOR, PFS, OS, cellular kinetics, and PRO/HRQOL

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CNS, central nervous system; CrCl, creatinine clearance; CY, cyclophosphamide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; HRQOL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; LVEF, left ventricular ejection fraction; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PRO, patient-reported outcome.

- Assessments
  - AEs, including NEs, were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, except for CRS, which was graded using the Lee 2014 criteria[2]
  - NEs were defined as investigator-identified neurological AEs related to liso-cel
  - Efficacy was evaluated by PET/computed tomography according to the Lugano 2014 criteria[8] based on investigator assessment
- The treatment-emergent AE (TEAE) period was defined as the time from initiation of liso-cel administration through and including 90 days after liso-cel administration
- Liso-cel infusion and monitoring were to be delivered in the outpatient setting; treatment and monitoring in the inpatient setting were at the investigator's discretion
- Patients were considered to be monitored as outpatients if liso-cel was administered in the outpatient facility or in the inpatient facility with subsequent discharge the same day at the end of the observation period (**Figure 2**)
- For outpatient monitoring, community specialty oncology centers were required to have HSCT or phase 1 study capabilities and a multidisciplinary medical team; patients were required to both have a caregiver and remain within 1 hour of the site for 30 days after liso-cel infusion
- One designated hospital capable of providing oncology care and 24/7 CAR T cell AE management was required

Figure 2. Outpatient liso-cel treatment and monitoring in OUTREACH



Results

Table 1. Baseline demographics and clinical characteristics

	Outpatients (n = 57)	Inpatients (n = 25)	Total (N = 82)
Age, median (range), y	65 (28–83)	69 (34–86)	66 (28–86)
≥ 65, n (%)	29 (51)	15 (60)	44 (54)
≥ 75, n (%)	11 (19)	5 (20)	16 (20)
Male, n (%)	39 (68)	15 (60)	54 (66)
Histology, n (%)			
DLBCL NOS	37 (65)	13 (52)	50 (61)
tDLBCL from indolent histologies	15 (26)[a]	1 (4)[b]	16 (20)
HGBCL[c]	4 (7)	11 (44)	15 (18)
Primary mediastinal B-cell lymphoma	1 (2)	0	1 (1)
Secondary CNS lymphoma, n (%)	0	2 (8)	2 (2)
ECOG PS of 0 / 1 at screening, n (%)	19 (33) / 38 (67)	8 (32) / 17 (68)	27 (33) / 55 (67)
No. of prior lines of therapy, median (range)	2 (2–4)	2 (2–6)	2 (2–6)
Received prior HSCT, n (%)	11 (19)	2 (8)	13 (16)
Refractory to last prior therapy,[d] n (%)	51 (89)	24 (96)	75 (91)
Chemotherapy refractory,[e] n (%)	47 (82)	21 (84)	68 (83)
LDH ≥ 500 units/L,[f] n (%)	15 (26)	8 (32)	23 (28)
SPD ≥ 50 cm², n (%)	17 (31)	13 (54)	30 (38)
CRP ≥ 20 mg/L,[f] n (%)	28 (49)	16 (64)	44 (54)
Received bridging therapy, n (%)	25 (44)	19 (76)	44 (54)

[a]Transformed from FL (n = 14) and Waldenström's macroglobulinemia (n = 1); [b]Transformed from CLL/SLL (n = 1); [c]Includes high-grade lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology; [d]Defined as best response of PR, SD, or PD to last systemic or transplant treatment with curative intent; [e]Defined as experiencing SD or PD to the last systemic or transplant treatment with curative intent patients received before coming on this study, or relapsed < 12 months after autologous HSCT; patients who were not chemotherapy refractory were considered chemotherapy sensitive; [f]Percentages are based on number of patients with nonmissing results.
CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; NOS, not otherwise specified; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the product of perpendicular diameters; tDLBCL, transformed diffuse large B-cell lymphoma.

- Baseline patient and disease characteristics were generally similar for outpatients and inpatients, respectively, except for the proportions of patients with tDLBCL from indolent histologies (26% vs 4%), HGBCL (7% vs 44%), SPD ≥ 50 cm² (31% vs 54%), and who received bridging therapy (44% vs 76%) (**Table 1**)
- The most common reasons for inpatient monitoring were disease characteristics (48%), including tumor burden and risk of AEs, and psychosocial factors (32%), including lack of caregiver support or transportation
  - Other reasons included COVID-19 precautions (8%), pre-infusion AEs (8%), including fever and vasovagal reaction, and investigator decision due to hospital experience with CAR T-cell therapy (4%)
- Median (range) follow-up from time of liso-cel infusion was 10.6 months (1.0–24.5) in the total population and 10.6 months (1.5–24.5) and 10.6 months (1.0–24.5) in outpatients and inpatients, respectively

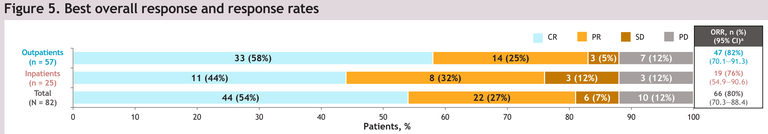
In patients with 3L+ R/R LBCL treated in the community setting, treatment with liso-cel demonstrated consistent safety with low incidences of severe CRS and NEs in both the outpatient and inpatient monitoring setting and durable responses with an ORR of 80%, CR rate of 54%, and DOR of 14.75 months with median follow-up of 17.35 months

Table 3. TEAEs of special interest

	Outpatients (n = 57)	Inpatients (n = 25)	Total (N = 82)
CRS or NEs, any grade/grade ≥ 3, n (%)	26 (46)/7 (12)	14 (56)/1 (4)	40 (49)/8 (10)
CRS, any grade/grade ≥ 3, n (%)	21 (37)/0	12 (48)/0	33 (40)/0
Median (range) time to onset of any-grade CRS, days	4.0 (1–9)	3.0 (1–9)	4.0 (1–9)
Median (range) time to resolution of any-grade CRS, days	5.0 (1–15)	4.5 (1–15)	5.0 (1–15)
NEs, any grade/grade ≥ 3, n (%)	16 (28)/7 (12)	8 (32)/1 (4)	24 (29)/8 (10)
Median (range) time to onset of any-grade NEs, days	8.0 (3–33)	7.0 (3–16)	7.5 (3–33)
Median (range) time to resolution of any-grade NEs, days	9.0 (1–47)	9.5 (3–35)	9.0 (1–47)
Treatment with tocilizumab and/or corticosteroids for CRS or NEs, n (%)	15 (26)	9 (36)	24 (29)
Tocilizumab only	1 (2)	3 (12)	4 (5)
Corticosteroids only	4 (7)	6 (24)	10 (12)
Both tocilizumab and corticosteroid	10 (18)	0	10 (12)
Hypogammaglobulinemia, any grade/grade ≥ 3, n (%)	8 (14)/0	3 (12)/0	11 (13)/0
Infections,[a] any grade/grade ≥ 3, n (%)	19 (33)/7 (12)	8 (32)/2 (8)	27 (33)/9 (11)
SPM, any grade/grade ≥ 3, n (%)	0/0	1 (4)/0	1 (1)/0
Grade ≥ 3 prolonged cytopenia at Day 29,[b] n (%)	19 (33)	8 (32)	27 (33)
Grade ≥ 3 decreased hemoglobin at Day 29, n (%)	6 (11)	3 (12)	9 (11)
Median (range) time to recovery to grade ≤ 2 in 8 patients,[c] days	5.5 (3–22)	22.0 (15–29)	9.0 (3–29)
Grade ≥ 3 decreased platelets at Day 29, n (%)	15 (26)	5 (20)	20 (24)
Median (range) time to recovery to grade ≤ 2 in 12 patients,[d] days	20.5 (5–39)	18.5 (8–29)	20.5 (5–39)
Grade ≥ 3 decreased neutrophils at Day 29, n (%)	9 (16)	6 (24)	15 (18)
Median (range) time to recovery to grade ≤ 2 in 13 patients,[e] days	12.5 (4–33)	8.0 (8–32)	10.0 (4–33)

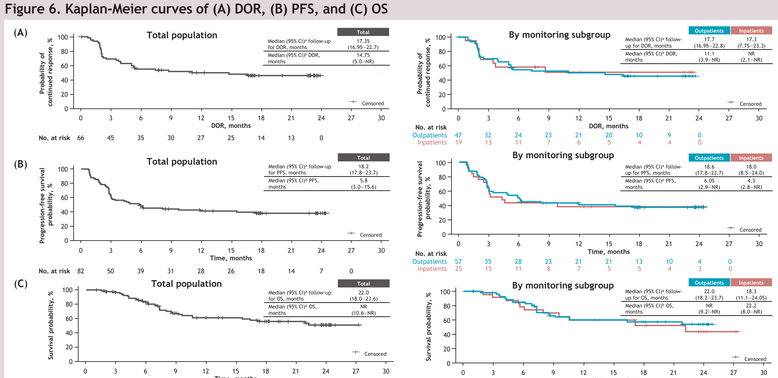
[a]Includes all TEAEs from the infections and infestations System Organ Class; [b]Any grade ≥ 3 laboratory results of anemia, neutrophil count decreased, or platelet count decreased at the Day 29 visit; [c]Recovery data are presented for the 6 outpatients and 2 inpatients who had hemoglobin laboratory results after Day 29; [d]Recovery data are presented for the 10 outpatients and 2 inpatients who had platelet laboratory results after Day 29; [e]Recovery data are presented for the 8 outpatients and 5 inpatients who had neutrophil laboratory results after Day 29.
SPM, second primary malignancy.

Figure 5. Best overall response and response rates



[a]Two-sided 95% exact Clopper-Pearson CIs. Percentages in the table may not match summed CR and PR rates in the bar graph due to rounding. CI, confidence interval; PR, partial response.

Figure 6. Kaplan-Meier curves of (A) DOR, (B) PFS, and (C) OS



[a]Kaplan-Meier method was used to obtain 2-sided 95% CIs; [b]Reverse Kaplan-Meier method was used to obtain median follow-up and its 95% CIs. NR, not reached.

Table 2. Study site characteristics

	Outpatients (n = 57)	Inpatients (n = 25)	Total (N = 82)
FACT (n = 10)	39 (68)	13 (52)	52 (63)
Non-FACT (n = 8)	18 (32)	12 (48)	30 (37)
Single entity[a] (n = 8)	26 (46)	17 (68)	43 (52)
FACT (n = 4)	13 (23)	7 (28)	20 (24)
Non-FACT (n = 4)	13 (23)	10 (40)	23 (28)
Dual entity[b] (n = 10)	31 (54)	8 (32)	39 (48)
FACT (n = 6)	26 (46)	6 (24)	32 (39)
Non-FACT (n = 4)	5 (9)	2 (8)	7 (9)
CAR T cell–naïve (n = 13)	20 (35)	6 (24)	26 (32)
Non-CAR T cell–naïve (n = 5)	37 (65)	19 (76)	56 (68)

[a]Single-entity sites included hospitals with outpatient infusion centers; [b]Dual-entity sites included oncology clinics with associated hospitals.
FACT, Foundation for the Accreditation of Cellular Therapy.

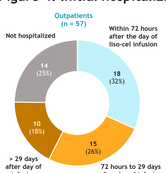
- Of 18 total sites, 44% were non-FACT, 56% were dual entity, and 72% had not previously treated patients with CAR T cell therapy (**Table 2**)
- Of 82 total patients treated with liso-cel, approximately one-third each were treated at non-FACT and CAR T cell–naïve sites, and nearly half were treated at dual-entity sites

Figure 3. TEAEs in ≥ 20% of patients (N = 82)

Safety

- The most common grade ≥ 3 TEAEs were cytopenias (**Figure 3**)
- The incidence of grade ≥ 3 TEAEs in outpatients versus inpatients was similar (74% vs 76%, respectively; data not shown)
- Thirty-three (40%) patients died on study, most because of disease progression. Of 5 reported deaths due to AEs, none were TEAEs; 4 occurred after the TEAE period and 1 occurred within the TEAE period in a patient who developed disease progression with colonic perforation, transitioned to hospice care and withdrew from the study, and died because of sepsis
- In the total population, no grade 3–4 CRS occurred and grade 3–4 NEs were low (10%); no grade 5 CRS or NEs were reported. Rates of any-grade CRS and NEs, median time to onset, and median duration were similar for outpatients and inpatients (**Table 3**)
- Tocilizumab and/or corticosteroid use for management of CRS or NEs was low, with similar rates of use between outpatients and inpatients (**Table 3**); no prophylactic corticosteroids were used.
- No macrophage activation syndrome, tumor lysis syndrome, or infusion-related reaction were reported (**Table 3**)

Figure 4. Initial hospitalization after liso-cel infusion



	Outpatients (n = 57)	Inpatients (n = 25)
Patients hospitalized, n (%)	43 (75)	25 (100)
Median (range) time to initial hospitalization, days	5.0 (2–310)	NA[a]
Median (range) duration of initial hospitalization, days		
All hospitalized patients	6.0 (1–28)	15.0 (3–31)
Patients hospitalized within 72 hours after the day of liso-cel infusion	9.5 (4–28)	NA[a]
ICU stays during initial hospitalization		
Patients admitted to the ICU, n (%)	1 (2)	2 (8)
Median (range) duration of ICU admission, days[b]	5.0 (5–5)	5.5 (4–7)

[a]Not applicable because inpatients are already hospitalized for monitoring. [b]For inpatients: days = date of discharge minus first liso-cel dose date plus 1. For outpatients: days = date of discharge minus date of admission after liso-cel administration plus 1. ICU, intensive care unit.

- Twenty-five percent of outpatients were never hospitalized after liso-cel (**Figure 4**)
- Reasons for initial hospitalization of outpatients were AEs in 35 (61%), including CRS (n = 18), CRS and NE (n = 1), febrile neutropenia (n = 5), fever (n = 3), infection (SARS-CoV-2 pneumonia, n = 1), and other AEs (n = 7); other reasons in 8 (14%)
- Of 18 (32%) outpatients hospitalized within 72 hours after day of liso-cel infusion, reasons for initial hospitalization were AEs in 16 (28%); other reasons in 2 (4%)
- Among inpatients, reasons for initial hospitalization were prophylaxis for CAR T cell administration in 19 (76%), AEs of fever in 2 (8%) patients; other reasons in 4 (16%)

Cellular kinetics/pharmacodynamics

- Median time to peak CAR T cell expansion was 10 days and similar in outpatients and inpatients
- The median peak CAR T cell expansion (C_{max}) was higher in outpatients compared with inpatients, but with considerable variability in C_{max} among patients
- Liso-cel showed long-term persistence in peripheral blood up to 2 years after infusion, with similar persistence profiles in both outpatients and inpatients
- Incidence of B-cell aplasia (< 3% $CD19^+$ B-cells in peripheral blood lymphocytes) was sustained in the majority (60%) of patients in the total population through Month 24, although sample size is limited after Month 6. For outpatients and inpatients, the incidence of B-cell aplasia was ≥ 86% and ≥ 96% through Month 6, respectively

Conclusions

- In the OUTREACH study, 82 patients with 3L+ R/R LBCL were treated with liso-cel and monitored for CAR T cell therapy–related toxicities at community medical centers in outpatient and inpatient settings using standard operating procedures and multidisciplinary teams
- Safety and efficacy outcomes were similar between outpatients and inpatients and consistent with results from TRANSCEND[7]
- No severe (grade ≥ 3) CRS events were reported and the incidence of severe NEs was low, as was tocilizumab and/or corticosteroid use for their treatment
- Liso-cel treatment resulted in an ORR of 80% and CR rate of 54%, with durable responses (median DOR, 14.75 months)
- Twenty-five percent of outpatients were never hospitalized after liso-cel infusion. Of outpatients requiring hospitalization, most were admitted more than 72 hours after the day of liso-cel infusion (median time to initial hospitalization was 5 days)
  - Shorter initial hospital stays in outpatients versus inpatients (median of 6.0 vs 15.0 days, respectively) suggest hospitalization burden could be reduced by outpatient monitoring at qualified sites, which could result in lower total costs
- Overall, these data support the feasibility of liso-cel treatment at community medical centers and monitoring in the outpatient setting

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Acknowledgments

- Thank you to patients, caregivers, investigators, and study personnel
- Study funded by Juno Therapeutics (Bristol-Myers Squibb Company)
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Emily Burke, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb

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